Fate of induced pluripotent stem cells following transplantation to murine seminiferous tubules.

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Public Summary:
Here we demonstrate that we can derive iPSCs with addition of the germ cell factor, VASA, and produce cells that efficiently form germ cells in vivo in a transplant model but do not form tumors.

Scientific Abstract:
Studies of human germ cell development are limited in large part by inaccessibility of germ cells during development. Moreover, although several studies have reported differentiation of mouse and human germ cells from pluripotent stem cells (PSCs) in vitro, differentiation of human germ cells from PSCs in vivo has not been reported. Here, we tested whether mRNA reprogramming in combination with xeno-transplantation may provide a viable system to probe the genetics of human germ cell development via use of induced pluripotent stem cells (iPSCs). For this purpose, we derived integration-free iPSCs via mRNA-based reprogramming with OCT3/4, SOX2, KLF4 and cMYC alone (OSKM) or in combination with the germ cell-specific mRNA, VASA (OSKMV). All iPSC lines met classic criteria of pluripotency. Moreover, global gene expression profiling did not distinguish large differences between undifferentiated OSKM and OSKMV iPSCs; however, some differences were observed in expression of pluripotency factors and germ cell-specific genes, and in epigenetic profiles and in vitro differentiation studies. In contrast, transplantation of undifferentiated iPSCs directly into the seminiferous tubules of germ cell-depleted immunodeficient mice revealed divergent fates of iPSCs produced with different factors. Transplantation resulted in morphologically and immunohistochemically recognizable germ cells in vivo, particularly in the case of OSKMV cells. Significantly, OSKMV cells also did not form tumors while OSKM cells that remained outside the seminiferous tubule proliferated extensively and formed tumors. Results indicate that mRNA reprogramming in combination with transplantation may contribute to tools for genetic analysis of human germ cell development.